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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/880,711	06/12/2001	Alejandro Abuin	LEX-0191-USA	5531

7590 02/23/2004

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/880,711	ABUIN ET AL.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 8 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 8 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicant's arguments filed November 24, 2003 have been fully considered but they are not persuasive. Claim 8 is pending. Claims 1-7 and 9 have been cancelled.

The rejection of claim 8, made in the office action mailed May 19, 2003, under 35 U.S.C. 112, second paragraph, has been overcome by applicant's amendment.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 8 remains rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons presented in the office action mailed May 19, 2003.

The specification does not set forth a specific, substantial, and credible asserted utility for a murine embryonic stem cell line comprising an engineered mutagenic sequence in a gene comprising an exon sequence disclosed in SEQ ID NO: 328. The specification does not disclose any gene that comprises the exon, nor does the specification describe the structure of the gene. There is no identification of an open reading frame, coding region, start codons, or stop codons with regards to SEQ ID NO: 328. Further the specification does not disclose a function of the encoded protein. Since the function of the gene is unknown and uncharacterized, cell cannot be used for any of the disclosed utilities.

Applicant argues that the described mutation was made using insertional mutagenesis that disrupts the normal transcription and splicing of the gene encoding the wild type form of the RNA binding protein. Applicant also argues that the mutagenesis protocol used in the presently claimed invention does not require any knowledge of gene structure in order to produce the claimed ES cell line. Applicant argues that concerns about the lack of disclosure of gene structure are irrelevant. Applicant argues that the claimed cell line was produced using a patented method and a patented vector. Applicant argues that

the claimed invention has uses in bioinformatics as well as in the design of gene specific primers useful in subsequent PCR analysis. Applicant argues that those skilled in the art could have searched SEQ ID NO 328 in the public databases to readily reveal the identity of the mutated gene. Applicant argues that a similar analysis was performed prior to producing knockout mice from the described cell line. Applicant argues that the fact that the specification does not teach the function of the gene highlights the basic motivation for and fundamental usefulness of the present invention. Applicant argues that if the gene's function were known, there would be no motivation for producing knockout mice. Applicant argues that the claimed cells were used to determine that the encoded protein plays a role in regulating circulatory homeostasis. These arguments are not persuasive.

There is no disclosure in the specification that any DNA sequence comprising seq id 238 encodes an RNA binding protein. Applicant should not make such assertions with backing them up with specific citations to the specification. Any such discovery of encoded protein function is not supported by the specification and thus cannot be used as evidence of utility at the time of filing. Applicant is also reminded that the claim is to a product and not a method of insertional mutagenesis. While the methodology and products used in the mutagenesis might be patentable, every product produced by that method has to meet the standards of utility on its own merits. Fundamentally, at the time of filing applicant did not know the function of the protein that was encoded by a DNA sequence comprising seq id no 238, and thus the claimed invention has no utility because of this. The function of the protein cannot be provided post-filing. In fact applicant admitted as much in stating that the cells were used to discover the encoded protein functions in circulatory homeostasis. Further, a search of public databases as part of the examination for the first office action resulted in a determination that there was no knowledge of this sequence at the time of filing. Ergo, the inability to find a reference teaching a DNA sequence that encoded seq id no

238 means that the public could not have searched the public databases to determine the encoded protein. Applicant's invention falls under the guise of "further research" that is in order to use the claimed ES cell line, which is disclosed as to be used in the production of knock out mice, addition investigation must be performed to determine the function of the encoded protein. In addition the specification does not describe any specific determinations to be used by analyzing or assaying the claimed ES cells, much less the mice produced from them. See MPEP 2107.01. Therefore, specification does not provide any uses for the claimed ES cell that indicate a specific or substantial utility. Again, it is emphasized that 1) utility cannot be established post-filing, and 2) the discovery post-filing of the protein's homeostatic role does not provide for utility at the time of filing. It is pointed out to applicant that many mice have been made where the function of the protein encoded by the gene was known prior to producing the mice.

Applicant argues that knockout mice have an inherent value in discovering the function of genomic sequence information. Applicant also argues that public and private efforts have spent several billion dollars to obtain human genomic sequence data and that this demonstrates that genomic sequence data has substantial and specific utility. Applicant argues that the present invention adds value to human genomic data by assigning critical function annotation to the human sequence data. Thus, applicant argues the invention obviously has substantial utility. Applicant argues that the NIH issued a request for applications for proposals to develop tools and techniques for the establishment of random and a targeted sequence-tagged insertion libraries of ES cells that could generate mutant mice. Applicant also argues that publicly funded gene trapping efforts exist and that this supports their allegations that the described invention has a well-established utility. These arguments are not persuasive.

The recognition by the art or the scientific community, as applicant has stated, does not mean that the products would inherently be useful. Further, such recognition is not a standard of utility. The standards of utility are determined on the disclosed uses of the claimed invention. MPEP 2107.01 defines "substantial Utility" as having a "real world" use. The MPEP further states that utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. MPEP 2107.01 defines "specific Utility" as specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. There is no mention of scientific or business interests in a particular area of endeavor, a request for proposals in a particular area of endeavor or money spent in a particular area of endeavor as evidence of utility. Applicant has provided no evidence that such recognition of these indicators exist. Perhaps all of this endeavor is in the hopes of making something that has utility, and not that any and all results have utility.

Applicant argues that there is no citation of art enabling an alternative means of discovering the specific physiological role of the presently mutated gene. Therefore, applicant argues, there is little question that the described genetically engineered mutations provide an exquisite resource for identifying the physiological role of the gene at issue. Applicant argues that the novel cells enable the discovery of the physiological/medical significance of the gene. These arguments are not persuasive.

In describing the claimed cells as providing a resource for identifying and discovering the physiological role of the gene, applicant has admitted that the cells require further research before the function of the gene can be known. The specification states the ES cells can be used to produce knock out mice, and states that as seq id no 328 was isolated from ES cells, this suggests a role for the encode protein in development. The clear implication is that the knock out mice is to be used as models of development. However, the specification

provides no guidance as to the endpoint of the assay. In other words the specification does not state specifically what phenotype is to be looked for, nor does the specification state how to look for the endpoint. Without knowledge as to the function of the encoded protein, a meaningful assay cannot be immediately put in the hands of public. The fact of the matter is that in order to use the ES cells and the resultant mouse, the artisan would need to do further research to determine the physiological function of the protein which comprises seq is no 328 can be discerned. Applicant's claimed cell line requires further research to determine its use and this fact alone indicates that the invention lacks utility.

Applicant argues that the claimed cell line is akin to bioengineered seeds. Applicant argues that the seeds are used to cultivate useful crops, and in a similar fashion the ES cells are cultivated into knock out animals. Applicant argues that there is no argument regarding the utility of knock out animals. These arguments are not persuasive.

In the instance of bioengineered cells, the crop cultivated would be known to contain a particular DNA sequence and the function of the protein encoded by the DNA sequence. Similarly, the knock out animal contains a disruption of a gene of known function, and the animal would have a specific phenotype that correlated to its disclosed used. Whereas in basic research, the function of the proteins encoded in bioengineered products might not be know, and the search for sun function might be the purpose of the experiments, this type of scientific endeavor is not patentable until the function of the protein is known and disclosed in the specification at the time of filing.

Applicant argues that genetically engineered cell lines have long been used by the academic community and Biotech industry to characterize biochemical pathways, in cancer screening and to produce therapeutic products. Applicant argues that there is broad acceptance of genetically engineered cell lines as having broad utility. Applicant argues that the claimed cells can be used in any one of these utilities, and that only one utility is

needed. Applicant argues that the claimed cells lines would have been recognized by the skilled artisan has having a broader utility as research tool lines. Applicant argues that the cell lines have an additional utility in producing live animals containing a genetic complement largely derived from the mutated ES cells. Applicant argues that the PTO has issued numerous patents utilizing technologies directly relating to the generation of ES cells. Applicant argues that there is no basis to argue that a novel mutated ES cell line that specifically enables the functional characterization of a specific gene lacks patentable utility. These arguments are not persuasive.

The specification does not disclose the use of the claimed ES cells in the analysis of biochemical pathways, in cancer screening or in the production of therapeutic products. Applicant does not disclose which pathways or the means to analyze them, does not disclose cancer screening, whether the screening is diagnostic or treatment, or what the assay endpoint is. Further, the use of ES cells in such processes is not a specific or substantial utility. Without knowledge of the function of the protein encoded by the DNA sequence comprising seq id no 328, there cannot be a "real-world" value or substantial utility to the ES cells as there is no immediate benefit to the public. Also there cannot be a specific utility as the description of the ES cells as useful in analyzing biochemical pathways, cancer screening or producing therapeutics does not provide any specificity as how the cells will be used. Applicant is referred to MPEP 2107.01.

In summary, as the function of the protein encoded by the DNA sequence or gene which comprises seq id no 328, the ES cells comprising a disruption of this DNA sequence or gene have no specific or substantial utility. The ES cells are subject to further research to determine the function of the encoded protein, and the ES cells are not described to be useful in any specific use. There is no immediate benefit to the public from the claimed ES

cells other than "use-testing" which has been found not to establish a utility (*Brenner v Manson*, 148, USPQ 689, 696 (US, 1966)).

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 8 remains rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons presented in the office action mailed May 19, 2003.

SEQ ID NO: 328 contains wild-cards ("n") or unknown nucleotides at several nucleotide positions. As such, these sequences are not considered to be described because the complete structure, that is nucleotide sequence, of SEQ ID NO: 328 cannot be envisioned. Further SEQ ID NO: 328 consists of 400 nucleotides in length. To one of skill in the art, these sequences are not of sufficient length that one would believe that they reflect a complete gene and no complete genes containing these sequences are described (for example, by structure, function, or location). As such, the claimed subject matter cannot be deemed adequately described by the specification such that skilled artisan would realize that applicant had possession of the mouse embryonic stem cell of claim 8. Therefore conception would not be achieved until reduction to practice has occurred outside of the specification. Adequate written description requires more than a mere statement that it is part of the invention. The nucleic acid sequence of the breadth of the claims required. See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

Applicant argues that the described method of preparing the ES cell requires the actual production and isolation of the ES cell clones prior to the generation of any sequence data. Applicant argues that seq id no 328 represents exon sequence that clearly identifies the gene that has been mutated in the described ES cell line. Applicant argues that those of skill in the art would understand that possession of the described ES cell line clone is prerequisite to obtaining the exons sequence of seq id no 328. These arguments are not persuausive.

Simply put, seq id no 328 contains wild-card nucleotides at several positions and there for the complete structure is not known. Even if the ES cells can be produced, there is no written description of seq id no 328, and thus no evidence of possession at the time of filing. Seq id no 328 is a critical element to the claimed invention and as such it must comply with the requirements of 35 U.S.C. 112, first paragraph.

Applicant has indicated that if written description is the remaining rejection, they will deposit the cell line. This is not persuasive.

The claim is to "an" ES cell line and not a specific ES cell line. For a deposit to overcome written description applicant would need to limit the claim to the cell line deposited, and assure that the specification supports that the particular sequence contained in the cell line. Otherwise, an issue of new matter will be raised.

Claim 8 remains rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial, and credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention for the reasons presented in the office action mailed May 19, 2003.

Applicant states that their arguments to the utility rejection overcome this rejection. This argument is not persuasive.

For the reasons given in rebuttal above to applicant's arguments, the claimed ES cell line lacks requisite utility to have an enabled use.

The claims are free of the prior art. At the time of filing, the art did not teach or suggest SEQ ID NO: 328, or a mouse embryonic stem cell line comprising an engineered mutagenic sequence in a gene comprising an exon sequence disclosed in SEQ ID NO: 328.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on 571-272-0408. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

February 18, 2004